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Management of Acute Febrile Illness: Doxycycline, the Empirical Antibiotic of Choice

Acute fever or acute febrile illness is one of the most common presenting complaints to the physicians in OPDs and in emergency care, in children and in adults alike. Fever itself is not a disease; it is both a symptom and a sign of disease.

India, being a tropical country, acute fever has myriad causes. Most fevers are infectious in origin due to bacterial, viral or parasitic protozoan infections notable among which are dengue, typhoid fever, malaria, Chikungunya, scrub typhus and rickettsial infections, Japanese encephalitis, leptospirosis, respiratory tract infections, sexually transmitted infections. The cause usually depends on the disease endemicity and seasonality of infections.

Such a diverse infectious etiology that often overlaps, presents a challenge to the treating physician. These infections often present with similar clinical features. A diagnosis is not always possible based on clinical presentation alone and correct diagnosis is reached only with specific diagnostic tests. Hence, a common approach to acute fever is the use of empirical antibiotics and adjunctive supportive treatment with antipyretics.

When choosing an empirical antibiotic, we do not want to miss deadly fevers such as scrub typhus, leptospirosis, the diagnosis of which requires expensive investigations. The cost of investigations in acute fever may run in hundreds and thousands, and the cost of empirical antibiotics may be less than one hundred rupees.

To understand the rationale of use of empirical antibiotics in a patient with acute febrile illness, a brief review of pathogenesis of fever is relevant here. The body temperature is determined by a balance between pyrogens and cryogens; pyrogens cause fever, cryogens are antipyretic. The febrile response is mediated by the release of endogenous pyrogens, which are cytokines. There are three main pyrogenic cytokines: Interleukin (IL)-6, IL-1, ciliary neurotrophic factor (CNTF) and tumor necrosis factor (TNF)- α , which are produced by neutrophils, macrophages and lymphocytes in response to exogenous pyrogens, which are mainly microorganisms or their toxins.¹ These pyrogenic cytokines stimulate the hypothalamus to raise the thermoregulatory set point resulting in increase in body temperature.

Elevated levels of cytokines are the hallmark of various bacterial and viral infections.² The use of agents that reduce cytokine production or their activity has thus been explored as a potential therapeutic option. The rationale of using antibiotics as anticytokine therapy comes from evidence, which has shown that antibiotics can modify cytokine production.³ These immunomodulatory effects inhibit production of proinflammatory cytokines.

A broad-spectrum antibiotic such as doxycycline can be a rational first choice of antibiotic in patients presenting with acute fever. It is bacteriostatic⁴ and also has anti-inflammatory activity including antiviral activity against herpes simplex virus, rotavirus and dengue virus.²

Doxycycline is effective for treating respiratory tract infections such as community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB).⁴ It has been used as chemoprophylaxis and treatment for malaria,⁵ sexually transmitted infections,⁶ management of acne vulgaris⁷ and is regarded as the drug of choice for scrub typhus⁸ and for rickettsial infections.⁹ Doxycycline has been used in patients with enteric fever and brucellosis.¹⁰ In endemic areas, antibiotic treatment of typhoid fever is usually empirical. Concurrent treatment with doxycycline may be required to cover for typhus and leptospirosis.¹¹

In addition, doxycycline may have a role in dengue fever because of its immunomodulatory effect in reducing the proinflammatory cytokines (IL-6 and TNF) and also due to its ability to inhibit replication of the dengue virus *in vitro*.¹² Disease severity in dengue virus infection has been linked to an increase in various cytokine levels.¹³ Therefore, by decreasing pro-inflammatory cytokine levels, doxycycline can provide a clinical benefit to dengue patients at high risk of complications.¹⁴

Updated recommendations from the American Academy of Pediatrics (AAP) now permit doxycycline for ≤ 21 days in children of all ages.¹⁵ Doxycycline binds less readily to calcium than other tetracyclines, and the risk of dental staining with short courses of doxycycline is minimal.

Another important point to be considered is that empirical antibiotic must also have a low probability of resistance. Most of us prescribe azithromycin or cefuroxime as empirical antibiotics in fever of duration more than 3 days. Penicillin till today is sensitive in streptococcal sore throat. Doxycycline is another antibiotic with low probability of resistance.¹⁶

Hence, while awaiting lab reports, if you want to prescribe an empirical antibiotic meanwhile, doxycycline appears to be a rational, safe and inexpensive choice given its proven effectiveness, fewer adverse effects, oral route of administration, once-daily dose, low probability of developing resistance and low cost,^{12,17} which is especially pertinent in a resource-poor setting as India.

REFERENCES

- Ogoina D. Fever, fever patterns and diseases called 'fever' - a review. *J Infect Public Health*. 2011;4(3):108-24.
- Garg P. Role of doxycycline in the management of dengue fever. *Indian J Clin Pract*. 2018;29(2):131-4.
- Bailly S, Fay M, Gougerot-Pocidallo MA. Effects of antibiotics on production of cytokines by human monocytes. *Pathol Biol (Paris)*. 1993;41(8 Pt 2):838-44.
- Holmes NE, Charles PG. Safety and efficacy review of doxycycline. *Clinical Medicine: Therapeutics*. 2009;1:471-82.
- Tan KR, Magill AJ, Parise ME, Arguin PM; Centers for Disease Control and Prevention. Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis. *Am J Trop Med Hyg*. 2011;84(4):517-31.
- Peyriere H, Makinson A, Marchandin H, Reynes J. Doxycycline in the management of sexually transmitted infections. *J Antimicrob Chemother*. 2017 Nov 22. [Epub ahead of print]
- Del Rosso JQ. Oral doxycycline in the management of acne vulgaris: current perspectives on clinical use and recent findings with a new double-scored small tablet formulation. *J Clin Aesthet Dermatol*. 2015;8(5):19-26.
- Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR Guidelines for diagnosis & management of Rickettsial diseases in India. *Indian J Med Res*. 2015;141(4):417-22.
- Thompson CN, Blacksell SD, Paris DH, Arjyal A, Karkey A, Dongol S, et al. Undifferentiated febrile illness in Kathmandu, Nepal. *Am J Trop Med Hyg*. 2015;92(4):875-8.
- Shafei AZ, Luka WS. Doxycycline in enteric fever and brucellosis. *Br Med J*. 1973;3(5870):50.
- Basnyat B. The treatment of enteric fever. *J R Soc Med*. 2007;100(4):161-2.
- Kanodia N, Khare DC. A randomized controlled study to assess the effect of doxycycline on IL-6 and TNF levels among the patients of dengue. *JMSCR*. 2018;6(2):1079-83.
- Zavala-Castro J, Fredeking T. Doxycycline modify the cytokine storm in patients with dengue and dengue hemorrhagic fever. *Int J Infect Dis*. 2010;14(Suppl 1):e44.
- Fredeking TM, Zavala-Castro JE, González-Martínez P, Moguel-Rodríguez W, Sanchez EC, Foster MJ, et al. Dengue patients treated with doxycycline showed lower mortality associated to a reduction in IL-6 and TNF levels. *Recent Pat Antiinfect Drug Discov*. 2015;10(1):51-8.
- American Academy of Pediatrics. Tetracyclines. In: Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds.). *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st Edition, Itasca, IL: American Academy of Pediatrics; 2018. p. 905.
- Cunha BA. New uses for older antibiotics: nitrofurantoin, amikacin, colistin, polymyxin B, doxycycline, and minocycline revisited. *Med Clin North Am*. 2006;90(6):1089-107.
- Joshi R, Kalantri SP. Acute undifferentiated fever: management algorithm. Available at: http://www.apiindia.org/pdf/monograph_2015_update_on_tropical_fever/001_acute_undifferentiated_fever.pdf. Accessed on October 30, 2018.